PROFESSOR: Today we're going to talk about the evolution of the earliest nervous systems, the evolution. Why were nervous systems so important with multicellular organisms? Single-cell organisms can do a lot, and they don't have nervous systems.

But remember they have primitive cellular mechanisms. They respond to inputs. The effects of inputs are conducted throughout the cell. They respond to cells. They do a lot of things multicellular organisms do. But as soon as you start putting a lot of cells together, then you have the problem of integration, one part of the organism with another.

OK. So what are some multipurpose actions that every animal, even one-cell organisms, must be able to perform? I teach animal behavior. And so this, to me, even though it's omitted by a lot of behavioral textbooks and teachers, to me, you've got to start with the fundamentals. What do our animals do?

AUDIENCE: Locomotion.

PROFESSOR: Locomotion, big one. You know, what do they use locomotion for? To escape from things, to get away from things, and to grab things, either attack them, and kill them, and eat them, or find food in some other way. It requires locomotion, unless--

There are a few exceptions. There are some animals that have evolved, at least at certain stages of their life, sessile forms, where they just sit. But most organisms have to locomote towards or away from things.

What else? What is another multipurpose action?

AUDIENCE: Reproduction.

PROFESSOR: Reproduction, very basic. But reproduction--

Well, that's a broader thing. I'm talking about fundamental action patterns. So let's go back from reproduction. But these things we're talking about are involved in reproduction. You're absolutely right. And that's particularly fundamental because that's what drives evolution. Yeah?

AUDIENCE: Responding to a stimulus?

PROFESSOR: Responding to a stimulus, very basic. But I want the action. How do they respond to the stimulus besides locomotion? Yes?

AUDIENCE: Orientation?

PROFESSOR: Orienting, turning. Animals have to respond to where things are. OK. So locomotion, approaching, avoiding, orienting towards or away again. And then I've added here exploring, or foraging, or seeking. But you see that's just includes the first two.

But what is included in foraging that's not necessarily in those first two, locomotion and orientation? There's an element that's involved. I think I probably asked that--

Yeah, here. That's the next question. OK? Approach and avoidance with flight movements are controlled by sensory inputs plus one other thing, one other important thing. What is that other thing? Very important in the evolution of the CNS.

AUDIENCE: Grasping?

PROFESSOR: Grasping is part of--

Yeah, grasping is actually a third fundamental action. But grasping isn't always. I'm thinking of something else. Anybody? Yes?

AUDIENCE: Motivation?

PROFESSOR: Motivation, the internal drive, something that comes from inside. I mean, why are they locomoting in one direction now and another direction another time? Why are they trying to get to food one time, to a mate another time, and so on and so forth?

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It depends on internal states. All right.

And then, as I mentioned, in that earlier slide-- we didn't get through everything there. But I asked a question about it here. What are the ongoing maintenance activities, or background activities, that are happening all the time? While their locomotion is happening, while the orienting is happening, whatever the motivation, it's independent of motivation. What are the ongoing background activities? And what kind of nervous system mechanism is involved? Yes?

AUDIENCE: Like homeostatic things, like [INAUDIBLE].

PROFESSOR: Yeah, things that need to be maintained in a constant state. That's good. Can anybody think of other things? Think of one you're doing one of these fundamental things. You're locomoting. You're going to your next class.

What are the background things going on? What is your body doing? What's it maintaining in homeostasis?

Temperature, for example. Even protists will seek places of the right temperature. They may not have much internal--

They're not endothermic, like we are. But they still have some kind of regulation. They still have to eliminate. They still have to--

What about a quadruped now, or a two or four legged animal? What does he do when he's locomoting? What is the maintenance?

AUDIENCE: Balance.

PROFESSOR: Balance. Yeah, posture. What are the mechanisms now that control these background things? What do we call them? They're lower level mechanisms for the most part. Many of them are spinal mechanisms, as we'll be talking about. Yes?

AUDIENCE: Reflexes?

PROFESSOR: A lot of them are reflexes, very simple, local pathways. That's exactly right. OK?

Simple reflexes and simple programs that are ongoing so they don't heart race, one.

The heart, of course, has its own ganglion that's regulating it. But it's influenced by the central nervous system also. It's adjusted because you need a lot more blood flow when you're running than you do when you're not running, things like that.

All right. So now let's start talking about conduction, nerve cells. How can conduction between cells occur without synaptic connections? We find such conduction before we find real neurons. It's found in sponges even, as well as in cnidarians, like hydra. Most of these things I'm going to talk about are found in little creatures, like hydra.

We used to call them the coelenterates. That's been revised. They're now the cnidarians.

But even sponges have conduction between cells. You touch a sponge, it's just not the cells that you're touching that are responding. Other cells respond too.

AUDIENCE: Like sort of electrical conductions, like that?

PROFESSOR: Yeah, there is a kind of electrical conduction. People sometimes call this conduction myoid and neuroid, just meaning it's like conduction between muscle cells. It's like conduction between nerve cells. But it's not really the same as in advanced organisms.

It's a term used in Nauta and [INAUDIBLE] book. And it's used by others that talk about primitive, conductive mechanisms. And it's done in the study of the anatomy of those creatures that we get ideas about earliest stages of nervous system evolution.

I've taken these pictures that I've put in the book not from George Parker at Yale, who was the guy who first tried to do it, but Mackie, George Mackie, who updated it, wrote a nice paper in *Quarterly Review of Biology* in 1970. This is his earliest stage.

There you have contracted cells that are also sensory. So they're sensory and

motor. They're responding to the environment. They can contract.

But he shows this--

He indicates this dashed line, where the membranes are against each other. That simply means gap junctions. It's something equivalent to gap junctions in our own nervous systems. It's electrical conduction working. Charged ions can flow from one cell to the other. So an electrical change that starts here can spread down the line.

And here's the second stage, where there are some contractile cells now that are no longer directly responsive to the environment. We call these the protomyocytes. They separate from the epithelium. They're below the epithelium. But you can see they're still joined to these epithelial cells by these gap junction-type contacts that allow the electrical changes in one cell to influence the cell that it's next to.

It's not like external conduction. The effect doesn't always spread to the entire organism. It often diminishes the further you get from the source.

And here, the contractile cells are no longer directly connected. To most of these cells, there are neurons in epithelium that are like neurons in that they have an axon process, an axon-like process that extends down to the muscle cells. The connections are still all electrical in nature. There's no chemical secretion yet triggering a response in the next cell.

He calls them protoneurons. They are epithelial cells. We have some primary sensory neurons that are just like this. We can talk about that in a minute.

And there is an electrical contact with the contractile cell, which are now completely sub-epithelial. Their only contact with the epithelium is through these axon-like processes. And then he has real neurons appearing, motor neurons with a chemical synapse. When he looked at hydra, he found things like evidence for chemical synapses contacting the contractile cells. And it was those cells then that got input from the epithelium.

Now you can call it a primary sensory neuron. So now you've got a two-synapse

nervous system. What was missing? Nauta studied the earlier--

He knew Mackie's work. He knew the George Parker work. He cites mainly Parker. But he realized there's something missing. There's no intermediate network. And so that's what I've added.

I added the question here. The addition emphasized by Nauta--

I'm sorry. I answered it for you. This is the picture then that Nauta added. So in Nauta's book, he has those earlier stages. And then he has cells in between sensory neuron. He has the axon now not directly contacting either a muscle cell or a motor neuron, but contacting a neuron in between.

So this is a neuron now that's not in direct contact with the environment outside. And it's not contacting improper cells. It is really an intermediate neuron. So we would define this is a motor neuron, of course the muscle cell. This we could call primary sensory. But then these are the intermediate. And that's the beginning of what Nauta refers to as the great intermediate network.

So now, let's define for every nervous system, including mammalian, primary sensory neuron, secondary sensory neuron, motor neuron, and intermediate network neuron. Just summarize. I've done it in a diagram.

But can you define them now? Remember, I want you to read before you come to class. You should already be able to do this. There's one person, three, two people that have not said anything yet. So speak up. Define just one of these. What's a motor neuron? Define any of them.

AUDIENCE: OK. So primary sensory neuron is the neuron that is in the epithelium. And if the first [INAUDIBLE].

PROFESSOR: OK. The primary sensory neuron. And what is it contracting? Where does its axon go?

AUDIENCE: To a secondary neuron.

PROFESSOR: To a secondary sensory neuron. And where is that one? Is it also in the periphery? No. The secondary sensory neuron is in the CNS. The primary sensory neuron is not. Major difference between those two types. Otherwise, what you said is completely right.

OK. Now, what about the motor neuron? I've defined it maybe three times so far in the class. In the corner, what is the motor neuron?

AUDIENCE: I'm actually not sure. I'm coming in to audit the class, and don't actually know much about it at all.

PROFESSOR: OK. OK. Well, if you don't want to answer it, somebody else. But if you come to the class, I do expect you to be able to answer some questions. OK? So somebody else. You want to go on?

AUDIENCE: [INAUDIBLE].

PROFESSOR: So define it again, the motor neuron. Where is the cell body of the motor neuron?

AUDIENCE: It is in the central nervous system.

PROFESSOR: In the central nervous system, and the axon goes out and contacts the muscles. Exactly. So that's how I came up with this diagram. There's one other cell type in here though. It's not primary sensory neuron. It's not secondary sensory neuron. It's not a motor neuron. Actually, there's two others.

There's cells like this. And even the second sensory neuron is sometimes included in that intermediate network. OK? But since we defined secondary sensory already, we'll include all the rest that are not motor neurons as intermediate network neurons.

And I should point out--

This is a good way to do it right now.

--that many neuroanatomists, when they talk about an interneuron, they always

mean a short axon interneuron, like these. Of course, I've greatly simplifies. I'm not showing the dendrites, simplifying the axon. But still, basically, that's the way a short axon interneuron connects.

But broadly speaking, these are all interneurons if they're not primary sensory and they're not motor. Everything else is an interneuron. We define secondary sensory separately. Most neuroanatomists would talk about the long axon cells in the central nervous system. They usually don't bother to call them interneurons, but they actually are. They just have much stronger axons.

OK. Now, we've got another cell type here. It's not in the central nervous system. It's in contact with a motor neuron, at least it's a neuron that looks like a motor neuron because its axon is leaving the central nervous system. What is it? It's in a peripheral ganglion. It's a preganglionic motor neuron here and a ganglionic motor neuron here. And the ganglionic motor neurons contact the smooth muscle, or gland cells, causing glandular secretions, causing contraction of the gut or some other organ.

AUDIENCE: So are they considered interneurons?

PROFESSOR: No. They are not. We call these environments here--

Of course, it's a type of interneuron. But it's defined as a motor neuron in contact with the central nervous system through a preganglionic motor neuron. We call this a motor because it's got an axon that causes some kind of movement or contraction or secretion. Secretion is considered an output.

So it's an output neuron. But it exerts its action through a peripheral ganglion. So it's synthetic ganglion or a parasynthetic ganglion, which we will be defining in more detail soon.

So just remember for me now the answer to question five. Where are neuronal cell bodies of the peripheral nervous system located? If you have cell bodies, and they're in the periphery, we say they are in a ganglion. OK?

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What about these words? What is a nerve? And what is a tract? And there are some other names we could add to that. But just take those two, nerve and tract. Define nerve for me. Anybody want to try?

AUDIENCE: A group of axons that have a common origin and [INAUDIBLE].

PROFESSOR: That's very good, except it's not always true. Many nerves don't have a common origin. They can be mixed. They can come from various sources. In fact, they might not even end up at the same place. That's not what defines them.

First of all, where is a nerve? In the periphery. If you hear people talking about nerves in the brain or the spinal cord, you'll know that they're not neuroanatomists, and they've never had this class. OK? Because we don't call them nerves unless they're in the periphery. OK?

In the central nervous system, we call them a tract or we give them some other name. We call them a bundle, a tract, a fasciculus, a lemniscus. All very descriptive terms of what these are like. Bundle, that's clear. OK.

Lemniscus means ribbon. So they're a ribbon of fibers. Fasciculus is basically a term meaning a group or bundle of axons. So they all mean bundles of axons. But you've got to keep separate the terms we use for central nervous system and peripheral nervous system.

So on this slide, I just put a bunch of these things. They're all defined in chapter three. There's a few things we haven't mentioned, like different cell groups. We call them ganglia outside the central nervous system. But in the central nervous system, yes, we violate our rules sometimes when we talk about the basal ganglia. That has to do with the history of the field. But usually, in the central nervous system, groups of cells that are functionality distinct or anatomically distinct, or usually both, we call them nuclei just to confuse you more because it doesn't-- in the nucleus of the cell at all. It's a grouping of cells. And we give them various specific names.

OK. We'll get to know the cord and neural tube very soon. What's the animal that is called in my book the simplest living chordate? There are others in the group, the

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cephalochordates. They have a similar structure, but there's this particular one--

[LAUGHTER]

PROFESSOR: Sorry. What did I do?

AUDIENCE: [INAUDIBLE].

PROFESSOR: Yeah.

AUDIENCE: [INAUDIBLE].

PROFESSOR: What's the animal that's pointed at both in this? Amphioxus.

AUDIENCE: There we go.

PROFESSOR: OK. And that little amphioxus can be found even in waters around here. It's very common. I may have said in the book that it was mostly southern waters, but we do now find them fairly far North as well. It has another name that's more common among systematic people who do systems in biology.

Well, chordate is the phylum. They are called the simplest living chordate. The branchiostoma is the other name. So when you look things up on amphioxus, you want to try searching both. But because amphioxus is so popular because it's so descriptive, meaning sharp at both ends. But still both are used, so I use both. You can see it is sort of sharp at both ends.

This is a picture of its nervous system. Notice it's not much bigger than it is anywhere. OK? It is a chordate.

So what is a chordate? What defines a chordate? We are a chordate.

I basically simplified a reconstruction done of amphioxus. It has, along the back, a nerve cord. That is its central nervous system. You can see it runs almost the entire length.

I've indicated, just to emphasize there, a very slight something different way at the

front end. Yes, it does have a brain. It's a little hard to make out if you don't study it with the microscope. But what is that?

It has no skeleton except that. It's another cord. It's not a nerve cord. OK? It's cartilage. It's called the notochord. And all chordates, at some stage in their development, usually at least early in development, have a notochord along the dorsal side. OK? That's the notochord.

And the dorsal nerve cord, or the central nervous system, develops in all chordates just above or just dorsal to that notochord. Notice it's got an odd spelling. It's like music, notochord. But that is the way it's spelled. OK.

So what does that central nervous system, that nerve cord, look like? This is another picture I simplified from a recent study. And I've shown in blue there the central nervous system. It's basically a tube with somewhat thickened walls. That's the neural tube with a ventricle in the middle, that you can't really see there very well.

But you do see purple nerves that are extending into that nerve cord. You also see outputs mostly on the ventral side here. And note that they're, unlike all the vertebrates, and we didn't notice in the early studies. Nah, they didn't know it actually because the electron microscopic reconstructions hadn't been done.

These are muscle cells. These are groups of muscles. And these are muscle processes that extend right up to the nerve cord. And they poke right into the nerve cord. And they directly contact the motor neurons in the ventral part of that nerve cord. That's a peculiarity of amphioxus.

OK. What's the Bell-Magendie Law? There's something in what I was just saying was almost getting to that. The Bell-Magendie Law, what is it? What do we usually call it more popularly and less historically? Discovered by Charles Bell and Francois Magendie. Bell, 1811. Magendie, 1823.

It was a discovery about mammals, about the nerves that come in and attach to the central nervous system, the spinal cord. They always divide into a dorsal root and a

ventral root as they approach the cord. The dorsal root contains actually the dorsal root ganglion cells. So we'll see pictures of that in a minute. Sensory fibers, the inputs coming into dorsally. The outputs, those axons are the motor neurons.

Remember in the picture of Cajal I showed you. The axons were growing out ventrally. OK? That's the ventral root. It's motor.

But then I ask you here. So that's the law of roots, the Bell-Magendie Law. Is it always true?

It's mostly true here. I mean, yeah, there are not actual axons going out. But the motor outputs are going out ventrally. The sensory inputs are coming in dorsally. But one thing really odd about amphioxus is one level of the nervous system, the nerves come in on one side, and they go out the other side.

You go to the next nerve. It does have multiple nerves. You see here are all the different roots.

The next segment down, you would find the input, the nerve from the periphery coming in dorsally, and the muscles being driven from the ventral part of the cord. So it alternates. Not only that, there are a few motor axons in that dorsal root. There are violations. And if you study other creatures in great detail, you will find even in higher vertebrates, you will find a few exceptions to the law of roots. But for the most part--

And you know, in neuroanatomy, it's not quite like physics, in case you're from physics or engineering. There are a lot of exceptions. And that's a lot of the times what we're describing is by and large true. So think of the Bell-Magendie Law that way. It's usually true.

What is it in primary brain vesicles? I indicated something odd here about the very front end. That's his brain. The amphioxus does have the beginning of primary brain vesicles. What are they?

We defined it before. I don't expect you necessarily to remember it. But now you've

read about it again because in chapter three. What are the three primary brain vesicles?

Now, I've added. I've told you there's three of them. Hindbrain, midbrain, and forebrain. OK. Those are the primary brain vesicles.

They generally are vesicles, in that they swell a little bit. They're a little bit bigger than the spinal cord below. And they usually get a little smaller at their boundary. So you can see a--

In brain development of human, and just about every other vertebrate, you do see three at least early in development.

Now, number 10 there asks for a little more detail. But this is another question that the answer would be the same for amphioxus and for mammals. In what subdivision of the CNS do visual inputs enter? Describe or name the two visual inputs found in many chordates.

The diencephalon, yeah, tweenbrain. Which of the brain vesicles is diencephalon in? Part of the forebrain. OK. It's the caudal part of the forebrain. It's not part of the cerebral hemispheres. They balloon out from the diencephalon.

So here's an amphioxus. This is from Allman. And he shows the arrangement of cells near there a little pigmented area, you see, right at the front end. And these are pigmented cells. Next to them are receptor cells responding to light. Next to them are neurons that have axons that travel to other parts of the nervous system.

The arrangement, that arrangement, that very simple arrangement in amphioxus is very much like the developing retina in vertebrates. Here's the pigment epithelium. Here are the receptor cells. Here are the neurons.

Receptor cells, they're really primary sensory neurons, very specialized for responding to light energy. And then the neurons in the retina, besides the interneurons, the main ones are the bipolar cells and the retina ganglion cells. And it's the ganglion cells that give rise to these long axons, just like these cells in

amphioxus. OK.

Now, these are cartoons of amphioxus on top and a kind of invertebrate on the bottom. It was based originally just on structural studies. But gene expression studies have shown now and confirmed that amphioxus has a region that expresses the genes of the spinal cord. He has a small region that expresses the genes of the midbrain, the segments of the midbrain, mainly one segment in invertebrates.

And then, more rostrally, the rest of it is like between brain. But he doesn't have the endbrain or an olfactory bulb. OK? The olfactory bulb is part of the endbrain in vertebrates.

And notice here there using the retina. It's ballooning out another kind of output gene, like the hemispheres, but now it remains part of the diencephalon. That's the retina. So there you have that visual area of the amphioxus. And here you have it in a vertebrate.

And here is the other area. Remember, I said there were two. Well, at the opposite side of the tweenbrain you have what we call an epithalamus. It's the most caudal segment of the developing tweenbrain. OK. That's where many chordates have a pineal eye, an eye on top of their head that responds to light. It's involved in control of photoperiodic behavior.

Even in us, that region controls the daily cycle of secretion of melatonin, even though it doesn't directly respond to light anymore. The animals we use in the lab, like the mouse, like a rat--

The mouse has got a pretty thin skull. And he's got cells there that actually do directly respond to light that gets through the skull. But the main inputs come through the lateral eyes, these eyes, through an indirect pathway.

OK. You should be able to summarize the basic rules of evolution. I do it on the next slide here. You should know the basic processes that govern evolution. And it's all right if you assume that natural selection, just like Darwin believed, is the major factor that causes gene sorting. Survival of some genes and not of others, the

decrease in the frequency of some genes, increase in the frequency of others. So I just summarized that. And I write it out in a pretty straightforward way in the book.

In the animal behavior class, I do talk a little bit about other mechanisms of genetic change that can result in changes outside of natural selection that still are important in evolution. There's various arguments about just how important those things are.

So when you think now about that very simple neural tube at the beginning of the central nervous system, you've got to say, how did that little worm-like animal, or animals like that, how did that end up evolving primates? You've got to think about the highest priority's evolution. And I've consistently done that through the book. And I've taken a nice phrase from Chandler Elliott, who wrote this book in '69. He has this phrase near the beginning of the book. "Every brain system grows logically from the tube."

What he simply meant was that, by small steps, by processes of natural selection, that neural tube developed the way we have it into current species. So it's mostly speculation. These are the questions I was following, just looking across the existing animals and also using some paleontology. So that's what we're going to do next time. We're going to talk about the ancestors of mammals. We'll sketch a simple premammalian brain.

Well, how could I guess what a premammalian brain is like? It's actually based mostly on an amphibian brain. OK? But we do have skulls of the group of animals that led to the evolution of mammals. They were running around the forest floor at the time of the big dinosaurs. They evolved with the dinosaurs. They were the cynodonts. OK?

We'll talk about that other stuff next time. These are the cynodonts. This is just a few of them. Reconstructed, we don't really know their colors. We just have the skulls.

But we do know a little about their brain because the inside of the skull preserves the shape of the central nervous system, just like we find the vertebrae, and we

know how big the spinal cord was. We know in brontosaurus is lumbar in large was probably bigger than his brain. But he was a very, very large animal, and he needed a lot of neurons there to control those enormous rear legs. But OK.

So we'll be talking about a brain that we'll assume--

If you don't like thinking in terms of evolution, you can think of it as an amphibian. But we think it's something like the early cynodonts. By the time you have the late cynodonts, they're pretty similar to mammals. OK? So that's what we'll be doing next time. And that's all the time we have.

AUDIENCE: Can you just go around and tell me the right names for things? Because I just want to make sure--